CP 2.1 History of Newborn Screening (NBS) and Summary of the NBS Process

History of NBS in California: In 1966 the NBS Program (NBSP), run by the Genetic Disease Branch (GDB) of the California Department of Health Services (CDHS) - began testing for Phenylketonuria (PKU) and in October, 1980, implemented testing for Galactosemia and Primary Congenital Hypothyroidism (PCH). Screening for sickle cell disease and related hemoglobin disorders were added in February, 1990. A pilot program for identification of Hemoglobin H disease was added in 1996 and officially became part of the NBS program in late 1999. In 2002 and 2003 a pilot program was initiated for additional metabolic disorders detectable by Tandem Mass Spectrometry (MS/MS) and in 2005, over 40 metabolic disorders and Congenital Adrenal Hyperplasia (CAH) were added to the screening panel. In July, 2007, Cystic Fibrosis (CF) and Biotinidase (BD) were also added to the screening panel. In 2010, a pilot program to detect Severe Combined Immunodeficiency (SCID) was implemented.

In July, 2007, the name of the GDB was changed to the Genetic Disease Screening Program (GDSP) and the CDHS was divided into two departments (California Department of Public Health and California Department of Health Services). The GDSP was re-organized into the California Department of Public Health (CDPH).

NBS Process: Prenatal care providers are required by state regulations to give the NBSP booklet, *Important Information for Parents about the Newborn Screening Test* (IIP) to pregnant women during their prenatal care visits. Because some women do not receive prenatal care, the same material is also distributed upon admission for delivery to a licensed perinatal health facility. The booklet is available in 11 languages and is provided at no cost from the GDSP, NBS Branch to prenatal care providers, hospitals, and county birth registrars.

A dried blood spot specimen is collected on a special filter paper attached to a Test Request Form (TRF). The birth hospital or licensed provider collects the sample between 12 hours of age and the sixth day of life. The blood sample, collected from the baby's heel, is spotted on the card and sent to one of seven pre-assigned regional screening laboratory approved by the state. These state-contracted Newborn and Prenatal Screening (NAPS) laboratories scan the TRF or manually enter demographic data from the TRF into the GDSP Screening Information System (SIS). They then review each specimen for adequacy.

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If the specimen is determined to be "adequate" or acceptable in quality and quantity, it is processed and tested. The results of the testing are also entered into SIS. A computer-generated written report of all test results, referred to as a "Result Mailer" , is mailed to the hospital where the specimen was collected as well as to the physician of record listed on the TRF.

NAPS laboratory staff report initial positive results for Galactosemia, Biotinidase Deficiency, Congenital Adrenal Hyperplasia, Hypothyroidism, or several of the disorders detected by MS/MS (including PKU), as well as any inadequate results by phone to one of the seven state-funded NBS follow-up coordination centers known as Area Service Centers (ASC). Additionally the labs enter a confirmation of contact (C of C) in SIS on each of these cases. The cases then appear on the ASC's Headline Case List in SIS. Positive Hemoglobin results are not called out, but appear on the headline case list after being reviewed at the Genetic Disease Laboratory (GDL) in Richmond. Similarly, positive screens for Cystic Fibrosis will not get called out to the ASCs but will appear on the ASC's Headline Case List.

The screening model for Cystic Fibrosis (CF) in California entails a four-step process. All newborn blood spots are tested for immunoreactive trypsinogen (IRT) at the regional NAPS Laboratory (Step 1). Newborns with values in the top 2.2% of the IRT distribution will have their blood spots tested at Stanford University for the presence of 40 different CFTR mutations (Step 2). Newborns with low IRT values or zero mutations are deemed to be screen negative for CF. Those with one mutation found will have one of their existing filter paper blood spots sent to Ambry Genetics for more sophisticated testing using DNA sequencing methods capable of detecting over 98% of all CFTR mutations (Step 3). Newborns with two or more mutations identified are screen positive for CF and, in conjunction with the newborn's primary care provider, will be referred to a CF Special Care Center for a diagnostic work up and sweat chloride test (Step 4). The parents of newborns with only one identified mutation will be sent a letter informing them that their baby is a carrier (as is one or both of the parents) and will be offered genetic counseling by telephone.

Once advised of a positive test, the ASC Coordinator/Program Specialist works with the newborn's physician and family to obtain a second blood sample or confirmatory test. Should a primary care provider wish to speak with a specialist, the Coordinator will make arrangements for consultation with an appropriate specialist consultant at any time during the process. In any case of a positive result, while the primary care physician is required to contact the family and arrange for necessary follow-up, the ASC NBS Coordinator/Program Specialist assists the physician with the process and sends the parents a letter that includes a pamphlet explaining the meaning of positive tests and the need for additional testing. A copy of this letter is also sent to the pediatric care provider.

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Confirmatory Testing

If the initial specimen is positive for any of the MS/MS disorders (amino acid, organic acid, and fatty acid oxidation disorders), other than PKU, the ASC NBS Coordinator contacts the primary care physician, assists with a referral to an NBSP-approved CCS Metabolic Center and recommends that confirmatory testing be done at the state-contracted metabolic confirmatory laboratory (Quest Diagnostics). The metabolic specialist must be listed on the Quest Test Request Form as the ordering physician; however, the primary care physician is often the one working with the family to arrange the specimen collection. If the physician decides to complete this testing at an outside lab, the results are to be reported to the NBSP by the physician via the assigned ASC.

- The confirmatory test for a sample that is positive for only PKU is a second filter paper sample which is run at the NAPS Labs.

- Samples that are borderline positive (6-10 ERU) for Biotinidase Deficiency will have a second filter paper run at the NAPS Lab. Samples (either the initial with a value of less than 6 ERU or the second specimen with a value of less than or equal to 10 ERU) will have a sample sent to Stanford for confirmatory testing.

- All confirmatory specimens for Galactosemia are sent to the state-contracted confirmatory laboratory Associated Regional and University Pathologists, Inc. (ARUP) in Salt Lake City, Utah.

- Confirmatory tests for hemoglobin disorders are sent to the state hemoglobin reference laboratory at Children's Hospital and Research Center at Oakland (CHRCO).

- Confirmatory testing for PCH and CAH is not provided by the Program and providers are required to have a venous blood specimen collected and tested at a private licensed laboratory (including hospital laboratories)**.** Test results are then to be reported to the NBS Program by the physician via the assigned ASC. The NBSP recommends that all confirmatory testing for these endocrine disorders be done in consultation with a specialist at a CCS Endocrine Center or CCS-paneled endocrinologist.

The NBS Coordinator/Program Specialist notifies the newborn's physician of the confirmatory test results. Because primary care physicians are often unfamiliar with these rare disorders, if a referral to a CCS center has not been made prior to recall/confirmatory testing, the Coordinator/Program Specialists assists the provider in referring a family to a California Children's Services (CCS)-Approved Metabolic or Sickle Cell Disease Special Care Center for additional testing, diagnosis, and treatment. The comprehensive team approach to care offered at CCS

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Special Care Centers is particularly important in treatment of all disorders screened for in the Program. The ASC NBS Coordinator or Program Specialist tracks all cases to ensure that appropriate follow-up occurs. When a physician is not available, or fails to obtain a recall or confirmatory specimen, the Coordinator contacts the family directly to help make the necessary follow-up arrangements. All contacts are documented in SIS and copies of letters and other notifications are kept in ASC files.

If the newborn screening specimen is considered to be "inadequate" or unacceptable, the hospital of birth or other licensed perinatal health facility/NBS provider that collected the specimen is notified by the region's ASC staff. It is the hospital's (or other licensed perinatal health facility/NBS provider) responsibility to ensure that a second specimen (retest) is collected in a timely manner. The ASC staff tracks all inadequate specimens to ensure a subsequent adequate specimen is obtained. Less than 1% of the samples are deemed inadequate by the NAPS laboratories.

If the specimen is collected prior to 12 hours of age (Early Specimen), a second specimen is also required because the test is not valid for certain tests if collected on a newborn less than 12 hours of age. These early specimens are also followed by the ASC until an appropriate sample is obtained and tested.

If the only NBS specimen is collected after a red cell transfusion, and there was no specimen obtained prior to the transfusion, the specimen will not be valid for galactosemia or hemogloginopathies and another specimen at least 24 hours post-transfusion will be recommended for hemoglobin testing.

In order to assure that all newborns are tested in a timely manner, hospitals are required to review all newborn charts 14 days from discharge to ensure they have received the NBS Result Mailer. If there is no Result Mailer and/or if there is no copy of the TRF in the record, these missing results are to be reported to the state (GDSP) within five days of discovery. Usually the state has a record of the baby having been tested and a duplicate mailer is forwarded to the hospital. Occasionally, it is found that a baby was discharged without being screened or the specimen lost in transit. Steps are then taken to assure that the baby is screened as soon as possible.

According to California law, it is the responsibility of the infant's primary care provider to ensure that a newborn screening test is performed and that the results are reviewed and noted in the patient's chart. Pediatric care providers who do not have a copy of the NBS Result Mailer can request a duplicate from the state (GDSP) or their regional ASC. Approximately 4,200 duplicate Result Mailers are sent out to physicians and hospitals every year.

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Note: If the requestor is the physician listed on the TRF, he/she can call 510-412-1541 and request a duplicate. If the requestor is NOT the physician listed on the TRF, a written request should be faxed to 510-412-1559, accompanied by a *Consent to Treat* from the physician's office signed by the parent or a *Consent for Disclosure and/or Release of Confidential Information or* the parent copy of the TRF signed by the parent.

Parents play an important and active role in close monitoring of these conditions and in implementation of treatment regimens consisting of special diets, and/or daily medications. To assist in parent education, the Newborn Screening Program has developed numerous educational materials that are available free of charge to health care providers. ASC NBS Coordinators provide assistance to GDSP in the development and field testing of educational materials.

Results of Testing: Between October 30, 1980 and December 31, 2008, the California Newborn Screening Program screened over 14,500,000 babies and identified over 11,500 cases of diagnosed disorders. With our current panel, we expect to identify over 800 children with one of the conditions screened for in a typical year.

The program has been very successful due in part to the active involvement of primary care providers in the follow-up of inadequate and positive test results. The ASC professional staff provides assistance to the primary care provider and all infants with non-negative results are tracked to ensure confirmation of diagnosis and initiation of a treatment plan.

Through this process, over 99% of the babies born in California are screened. However, a small number of newborns do fall through the cracks despite all the checks and balances of the program. Approximately 1,000 babies (0.5% of the births) are not screened at birth, another 125 with inadequate results of the initial test never receive a second test, and a very small number of infants with an initial positive test results are lost to follow-up. Therefore, it is critical that pediatric care providers review the newborn screening results on every infant in their care. If a child is under one year of age and has no record of the NBS test in the chart, a request should be made to GDSP Newborn Screening Branch for a copy of the Result Mailer.

If there is no record of screening, a specimen should be collected and submitted to the Program for testing. ASC staff can assist in this process.

The Program has numerous quality improvement, educational, and monitoring mechanisms in place to assure that all infants are screened and that the results are valid. However, biological variability, transfusions, and human error can result in missed cases. Errors can occur at the collection site, when the specimens are in transit, at the laboratory, in the computer processing of results and/or the reporting process.

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Therefore, **the possibility of a disorder should never be ruled out solely on the basis of the NBS results.** Any signs or symptoms of a disorder should be followed up immediately. To evaluate the completeness and effectiveness of the NBS Program, California law requires that all physicians making a diagnosis of a heritable disorder for which testing is required through the NBS Program, report such diagnosis to GDSP. GDSP will then investigate the case to determine if changes in policies or procedures for NBS are necessary.

Associated Document:
2.1.1 Newborn Screening Process Flow Diagram

